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[54] RADIOACTIVE DIAGNOSTIC AGENT AND NON-RADIOACTIVE CARRIER THEREFOR [75] Inventors: Makoto Azuma, Takarazuka; Masaaki Hazne, Amagasaki, both of Japan [73] Assignee: Nihon Medi-Physics Co., Ltd., Hyogo, Japan [21] Appl. No.: 324,903 [22] Filed: Nov. 25, 1981 Foreign Application Priority Data [30] Nov. 27, 1980 [JP] Japan A61K 43/00; A61K 49/00 [51] Int. CL3. U.S. CL

. 424/1.1; 424/9 ... 424/1, 9 [58] Field of Search

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ABSTRACT [57]

A 99mTc-labeled radioactive diagnostic agent being useful for visualization and dynamic inspection of hepatobiliary ducts and having a high stability and no materisl toxicity, which comprises 99mTc in the form of pertechnetate and a non-radioactive carrier, the nonradioactive carrier comprising an N-pyridoxyl-α-amino acid of the formula:

wherein R1 and R2 are each an atom or an atomic group present in the a-amino acid residue encompassed by the dotted line and R3, R4, R5 and R6 are each a hydrogen atom, a halogen atom, a C1-C10 alkyl group or a C1-C10 alkyl group substituted with at least one hydrophilic group or its salt, and a reducing agent for pertechnetate.

12 Claims, No Drawings

RADIOACTIVE DIAGNOSTIC AGENT AND NON-RADIOACTIVE CARRIER THEREFOR

The present invention relates to a 99mTc-labeled radi- 5 oactive diagnostic agent and a non-radioactive carrier therefor. More particularly, it relates to a novel 99mTclabeled radioactive diagnostic agent being useful for visualization and dynamic inspection of hepatobiliary ducts and having a high stability and no material toxic- 10 particularly useful for examination of hepatobiliary ity, and a non-radioactive carrier therefor.

For the purpose of non-invasive, dynamic inspection of hepatobiliary ducts, there have been used 131I-labeled radioactive diagnostic agents such as 131 I-labeled bromosulfophthalein (131I-BSP) and 131I-labeled Rose 15 Bengal (131 I-RB). However, 131 I emits β -ray and has a long half life (i.e. about 8 days) so that those radioactive diagnostic agents result unfavorably in giving remark-

able radiation exposure for patients.

Since 99mTc emits only γ-ray of about 140 KeV and 20 has a short half life (i.e. about 6 hours), it is quite suitable as a nuclide for radioactive diagnostic agents to be administered to human bodies. Because of this reason, attempts have been made to provide 99mTc-labeled radioactive hepatobiliary diagnostic agents, of which 25 examples are 99mTc-penicillamine, 99mTc-2-mercaptoisobutyric acid, 99mTc-N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid (99mTc-HIDA), etc. However, these conventional radioactive diagnostic agents are not satisfactory in their disappearance rate 30 from the blood, their transfer rate from the liver into the gall bladder, their excretion percentage into the urine, their stability and toxicity, etc.

Recently, it was found that pyridoxylideneaminates labeled with 99mTc have excellent properties suitable for diagnosis of hepatobiliary ducts [Kaku Igaku, 14, 927 (1977); J. Nucl. Med., 19, 397 (1978)]. Among them, 99mTc-labeled pyridoxylidene-isoleucine was actually hepatobiliary diagnostic agent has been highly evalu-

ated.

As a result of the extensive study, it has been found that the complex formed from an N-pyridoxyl-a-amino acid and 95 To shows chamical and biological behaviors in mammals similar to those of the complex formed from the corresponding N-pyridoxylidene-α-amino acid and 99mTc. For instance, their chromatographic behavior and distribution in mammalian bodies are extremely similar to each other. Advantageously, an Npyridoxyl-α-amino acid is more stable than the corresponding N-pyridoxylidene-a-amino acid within a wider range of pH, and therefore the former is more suitable for a carrier than the latter. This invention is based on the above finding.

According to the present invention, there is provided 55 a non-radioactive carrier to be used in diagnosis in nuclear medicine which comprises an N-pyridoxyl-a-

amino acid of the formula:

wherein R1 and R2 are each an atom or an atomic group present in the α-amino acid residue encompassed by the dotted line and R3, R4, R5 and R6 are each a hydrogen. atom, a halogen atom (e.g. chlorine, bromine, iodine, fluorine), a C1-C10 alkyl group (e.g. methyl, ethyl, propyl, butyl, pentyl, octyl) or a C1-C10 alkyl group substituted with at least one hydrophilic group or its salt, and a reducing * sent for pertechnetate.

There is also provided a radioactive diagnostic agent, ducts, which comprises 99mTc in the form of pertechne-

tate and the non-radioactive carrier.

Among the said symbols, R1 and R2 can each represent any atom or atomic group which may be present in the a-amino acid residue encompassed by the dotted line. Examples of such atom and atomic group are hydrogen, C1-C10 alkyl, C1-C10 alkyl substituted with at least one of amino, imino, nitro, hydroxyl, mercapto, C1-C10 alkoxy, C1-C10 alkylthio, carboxyl, oxo, thio, carbonamido, phenyl, etc., amino, imino, nitro, hydroxyl, mercapto, C1-C10 alkoxy, C1-C10 alkylthio, carboxyl, oxo, thio, carbonamido, phenyl, etc. Thus, the said atom or atomic group may be any one which is present in alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamine, glutamic acid, glycine, histidine, hydroxylysine, hydroxyproline, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, proline, serine, taurine, threonine, thyrosine, tryptophan, tyrosine, valine, etc. As the hydrophilic group which may be present on the alkyl group represented by R3, R4, R5 or R6, there are exemplified —SO3H, —SO3M, —OSO3H, —OSO3M, —COOM, —NR3X, —COOH, —NH2, —CN, —OH, -NHCONH₂, -(OCH₂CH₂)₈-, etc. (in which M is 35 an alkali metal atom or an ammonium group, X is a halogen atom, R is a C1-C10 alkyl group and n is an optional integer).

The non-radioactive carrier of the present invention comprises as the essential components at least one of the subjected to clinical examination, and its utility as a 40 N-pyridoxyl-a-amino acids of the formula (I) and their salts and at least one of the reducing agents for per-

technetate.

The N-pyridoxyl-a-amino acids of the formula (I) may be manufactured by various procedures, among which a typical example is representable by the formu-

wherein R1, R2, R3, R4, R5 and R6 are each as defined above. Namely, the a-amino acid (A) and the pyridyl-

ketone (B) are condensed, follo ed by hydrogenation of the resulting Schiff base (C) to give the pyridoxyl-aamino acid (I). The condensation is usually carried out in the presence of a base such as potassium hydroxide in an inert solvent such as anhydrous methanol, and the 5 subsequent hydrogenation may be accomplished by catalytic hydrogenation in a conventional manner [J. Am. Chem. Soc., 70, 3429 (1948)].

Among various N-pyridoxyl-a-amino acids (I), preferred are those wherein R3 and R5 are each hydrogen, R4 is hydroxymethyl and R6 is methyl. While R1 and R2 can each represent any atom or atomic group which exists in the residue of a natural or artificial a-amino acid encompassed by the dotted line in the formula (I), their preferred examples are hydrogen, lower alkyl (e.g. methyl, isopropyl, 1-methylpropyl, 2-methylpropyl), carboxy(lower)alkyl (e.g. 2-carboxyethyl), hydroxy(lower)alkyl (e.g. hydroxymethyl, 1-hydroxyethyl), phenyl(lower)alkyl (e.g. benzyl), hydroxyphenyl(lower)alkyl (e.g. 4-hydroxybenzyl), etc. The term "lower" is intended to mean an atomic group having not more than 8 carbon atoms.

One of typical examples of the N-pyridoxyl-a-amino

$$R^{12}$$
 R^{12}
 R^{7}
 R^{1}
 R^{1}
 R^{1}
 R^{1}
 R^{1}
 R^{2}
 R^{2}
 R^{2}
 R^{3}
 R^{4}
 R^{4}
 R^{4}
 R^{4}
 R^{5}
 R^{7}
 R^{1}
 R^{1}
 R^{1}
 R^{1}
 R^{2}
 R^{3}
 R^{4}
 $R^$

wherein R7, R8, R9, R10, R11 and R12 are each a hydrogen atom, a halogen atom, a C1-C5 alkyl group or a C1-C5 alkyl group substituted with at least one hydrophilic group. Particularly preferred is the one of the formula (II) wherein R7, R4, R9, R11 and R12 are each hydrogen and R¹⁰ is hydrogen or methyl.

Depending upon the kinds of R¹, R² and R³, the carbon atoms to which those groups are attached may be asymmetric carbon atoms. In such case, there may be present four kinds of optical isomers or diastereomers, i.e. RR-, RS-, SR-and SS-forms. Any of these 50 isomers and their mixtures can be equally used in the non-radioactive carrier of the invention.

Examples of the salts of the N-pyridoxyl-a-amino acids (I) are the salts formed with organic or inorganic cations such as sodium ion, potassium ion and ammo- 55 nium ion, the salts formed with inorganic acids such as hydrochloric acid, nitric acid, sulfuric acid and phosphoric acid, the salts formed with organic acids such as acetic acid and oxalic acid, etc.

As the reducing agent for pertechnetists, there may cobe used any stannous salt chosen from stannous halides (e.g. stannous chloride, stannous fluoride), stannous sulfate, stannous nitrate, stannous acetate, stannous citrate, stannous tartrate, etc. Any other reducing agent which can convert heptavalent technetium into any 65 lower valent technetium is also usable insofar as its administration to mammals does not produce any material toxicity. Examples of such other reducing agent are

Shydride, lithium aluminum cuprous salts, sodium & hydride, etc.

On preparation of the non-radioactive carrier of the invention, the said essential components, i.e. the N-pyridoxyl-a-emino acid (I) or its salt and the reducing agent for pertechnetate, may be mixed in an optional order. The non-radioactive carrier may be in a solid preparation form such as powder or hyophilized powder or in a liquid preparation form such as aqueous solution. The pH of the non-radioactive carrier is not limitative, but it is preferred to adjust the pH within a range of about 3 to 10, particularly of about 6 to 9, for instance, by the use of an acid (e.g. hydrochloric acid) or an alkali (e.g. sodium hydroxide).

In addition to the said essential components, the nonradioactive carrier may include any conventional additive such as an antioxidant (e.g. ascorbic acid, erythorbic acid, gentisic acid), an isotonization agent (e.g. 20dium chloride) or a preservative (e.g. benzyl alcohol).

The molar ratio of the N-pyridoxyl-a-amino acid (1) or its salt and the reducing agent for pertechnetate in the non-radioactive carrier is usually within a range of I to 100, preferably of 3 to 30. The reducing agent may be used in a sufficient amount to reduce 99mTc in the acids (I) is an N-pyridoxyl-tryptophan derivative of the 25 form of pertechnetate present in the 99m Tc-labeled radioactive diagnostic agent prepared by the use of the non-radioactive carrier. When the stability of the nonradioactive carrier is taken into consideration, the reducing agent may be employed in such an amount as 30 being left at a concentration of 0.1 to 5 mmol/L after the preparation of the 99mTo-labeled radioactive diagnostic agent.

For preparation of the 99mTc-labeled radioactive diagnostic agent, 99mTc in the form of pertechnetate 35 may be contacted with the non-radioactive carrier. 99. To in the form of pertechnetate is used normally in its aqueous solution, which may include additionally any conventional additive such as a preservative (e.g. benzyl alcohol) or an isotonization agent (e.g. sodium chloride). While the concentration of 99mTc in the squeous solution as the 99mTo-labeled radioactive diagnostic agent is not particularly limited, it should have such a concentration as can afford a sufficient radioactivity econsistration for discreasing bepatobility ducts, prefa. Wy figure there 0.1 to 50 mCi in about 0.5 to 5.0 ml at the time of a finialistration.

As the result of the combination of the non-radioactive carrier in an aqueous solution form with an aqueous solution comprising 99mTc in the form of pertechnetate, there is prepared the 99mTc-labeled radioactive diagnostic agent in situ.

The non-radioactive carrier of the present invention has the following advantageous characteristics:

(1) The carrier is quite stable within a wide range of pH so that it can be stored for a long period of time after the preparation;

(2) The carrier can afford a 99mTc-labeled radioactive diagnostic agent by a simple operation, for instance, by contacting an aqueous solution comprising 99mTc in the from of perceives to the re-fifty

(i) The extrict is materially non-toxic, etc.

Further, the 99mTc-labeled radioactive diagnostic agent prepared by the use of such carrier has the following meritorious features:

(a) The diagnostic agent is stable for a sufficiently

long period of time after the preparation;

(b) the labeling efficiency of 99mTc is extremely high (e.g. 98% or more);

(c) when intravenously administered, the diagnosis agent is smoothly taken into the liver, transferred to the gall bladder and then passed through the bile duct to the small intestine so that the inspection can be accomplished within a short period of time;

(d) the radiation exposure for patients is smach reduced in comparison with ¹³⁴I-labeled radioactive hepatobilizry diagnostic agents;

(e) the toxicity is quite low, etc.

The **To-beled radioactive diagnostic agent may to be administered to patients in an amount sufficient to produce radioactivity necessary for examination of hepatobilisry ducts by an appropriate route. For instance, the intravenous administration of the **To-beled radioactive diagnostic agent of about 1 to 3 ml in volume having a radioactivity of about 1 to 5 mCl to a patient is quite suitable for hepatobilisry diagnosis.

Practical and presently preferred embodiments of the present invention are illustratively shown in the following Examples.

EXAMPLE 1

Preparation of a non-radioactive carrier by the use of N-pyridoxyl-L-tryptophan and stannous chloride (hereinafter referred to as "PLTSnA")

into sterilized water containing no pyrogen sub stance, germfree nitrogen gas was introduced to climiaute oxygen dissolved therein. Into the resulting water (300 ml), L-(+)-escorbic acid (334 mg) was dissolved, 30 and N-pyridoxyl-L-tryptophen [J. Am. Chem. Soc., 70, 3429 (1948)] (1999 mg) was suspended therein. To the resultant suspension while stirring, 2 N sodium hydroxide solution (2.3 ml) was gradually added to make the spending particles dissolved completely. The resulting solution was adjusted to a pH of about 7 with 2 N hydrochloric acid, and anhydrous stannous chloride (48 mg) was dissolved therein while stirring. The resultant solution was adjusted to pH 8.20 with 2 N sodium hydroxide solution and/or 2 N hydrochloric acid, 40 whereby a coloriess, transparent solution, i.e. the nonradioactive carrier "PLTSaA," was obtained. The nonradioactive carrier "PLTSaA" (1 ml) was filled in a vial through a filter of 0.22 µ in pore size in mitrogen atmo-Sphere

EXAMITUE I

Preparation of a ***To-labeled radioactive diagnostic agent using the non-radioactive carrier "PLTSaA" (hereinafter referred to as "To-(PLTSaA)")

In a vial flushed with sitrogen gas, the non-radioactive carrier "PLTSnA" (1.0 ml) was admixed with a physiological saline solution containing "ParTc (10 mCl) in the form of sodium pertechnetate (1.0 ml) and stirred well. The vial was heated in a bath of boiling water for 35 minutes and then cooled in a water bath at room temperature to make a coloriess, transparent solution as the "ParTo-labeled radioactive diagnostic agent "To-(PLTSnA)."

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layer chromatography using a silica gel thin layer plate and a mixture of methyl ethyl ketone, methanol and 2 M potassium chloride solution (10:9:1 by volume) as a developing solvent. Scanning with a radiochromatogram acanner revealed the presence of a single spot having radioactivity at Rf=0.62, and any other radioactive peak was not recognized.

Since, in the above the constagraphy system, **MarTc in the form of pertechnetate is to be developed to Rf=0.96 and a **MarTc-labeled tin colloid is to be retained at the original point, the presence of a single radioactive spot at Rf=0.62 means that the labeling efficiency is 100%.

EXAMPLE 1

Distribution of the ***To-lebeled radioactive diagnostic agen **To-(PLTSaA)** in the organs of rats

The ProTo-labeled radioactive diagnostic agent "To-(PLTSAA)" (0.2 ml) was administered intravenously to S.D. (Sprague-Dewicy) strain female rats. Pive minutes or 1 hour after the administration, the animals were excisioed, and various organs were taken out and subjected to measurement of radioactivity. The results are shown in Table 1.

TABLE I

Liver (1.74 0.79

Small intestine (0.12 04.13

Large intestine 0.49 0.07

Smeach 0.11 0.08

Spinon 0.04 0.04

Long 0.31 0.07

Smeat 0.07 0.02

Eidenya 0.16 0.21

Shood (1 mi)* 0.16 0.021

Caronn 14.12 1.34

Shodder (Urine) 0.76 2.45

Name "Books would controlled to 300 grant.

The above results show that the ***To-labeled radioactive diagnostic agent *To-(PLTSnA)** is uneful as an excellent radioactive diagnostic agent for examination of hepatobiliary ducts.

EXAMPLE 4

Stability of the non-redisective cerrier "PLTSeA"

The non-radioactive carrier "PLTSAA" as prepared in Flora of 1 were stored at 1' to 6' C. under the state of presentation from light for a period of 30 or 100 days. By the tea of the roll logic model active a color, a first labeled radiooctive diagnostic agent "To-(PLTSaA)" was prepared as in Example 2. The labeling efficiency was confirmed to be 100% in both cases (i.e. after 30 days storage and after 100 days storage). The distributions in the organs of rate when tested as in Example 3 are shown in Table 2 wherein the values indicate those 1 hour after the administration.

TABLE 2

Distribution of To—(PLTBsA) in organs of cuts (% to redicectivity administered; previag for 5 points)

	After an	persion	
Organa	90 days	100 days	
	1 - 5	6.71	
August a S. Contra	\$2.72	10.00	
Large beauting	0.04	643	
Stomeck	0.09	0.04	
Sphoon	0.06	0.07	
Long	0.06	0.07	
Heart	0.03	out .	
Kidneys	0.23	0.25	
Blood (1 ml)*	0.023	0.034	
Carcass	1.46	1.50	

TABLE 2-continued

Distribution of To-(PLTSnA) in organs of rats (% to radioactivity ada average for 5 animals)

	After pro	eperation	
Organs	50 days	100 days	
Bladder (Urine)	2.92	2.89	

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> From the above results, it is understood that the nonradioactive carrier "PLTSnA" is stable even after the storage at 3° to 6° C. for a period of 100 days or more.

EXAMPLE 5

Stability of the 99mTc-labeled radioactive diagnostic agent "Tc-(PLTSnA)"

(PLTSnA)" as prepared in Example 2 was stored at room temperature under the state of prevention from light for 24 or 48 hours. Then, the distribution of the resulting diagnostic agent in the organs of rats was examined as in Example 3. The results are shown in 25 Table 3 wherein the values indicate those 1 hour after the administration.

TABLE 3	
Distribution of To-(PLTSnA) in organs of	3
rats (% to radioactivity administered;	
average for 5 animals)	
After preparation	

51C1-01 7 C1-101			
	After preparation		
Organs	24 hours	48 hours	
Liver	0.89	0.82	
Small intestine	9331	93.62	
Large intentine	0.06	0.05	
Stomach	0.09	0.07	
Splece	0.05	0.06	
Long	0.09	0.08	
Heart	0.03	0.04	
Kidacys	0.27	0.29	
Blood (1 ml)*	0.026	0.024	
Стист	1.86	1.74	
Eladder (Urine)	2.9%	2.74	

te: "Body tweight normalized to 300 genus.

From the above results, it is understood that the 99mTc-labeled radioactive diagnostic agent "Tc-(PLTSaA)" is stable even after stored at room tempera- 50 ture for 48 hours or more. Since the half life of 95 Tc is about 6 hours, the assurance of the stability for a period of about 24 hours is sufficient for the practical use of the 99mTc-labeled radioactive diagnostic agent.

EXAMPLE 6

Preparation of non-radioactive carriers using the N-pyridoxyl-a-emino raids (f) other than N-pyridoxyl-L-tryptopi.an

In the same manner as in Example 1 but using N-pyridoxyl-L-isoleucine, N-pyridoxyl-L-phenylalanine or N-pyridoxyl-DL-5-methyltryptophan prepared by a conventional procedure [J. Am. Chem. Soc., 70, 3429 65 (PLTSaA)," (1948)] in place of N-pyridoxyl-L-tryptophan, there was prepared the non-radioactive carrier "PLISnA," "PLPSaA" or "PDLMTSaA."

EXAMPLE 7

Preparation of a 99mTo-labeled radioactive diagnostic agents using the non-radioactive carriers obtained by 5 the use of the N-pyridoxyl-α-amino acids (I) other than N-pyridoxyl-tryptophan

In the same manner as in Example 2 but using the non-radioactive carrier "PLISaA," "PLPSaA" or "PDLMTSnA" in place of the non-radioactive carrier "PLTSnA," there was prepared the 99mTc-labeled radioactive diagnostic agent "To-(PLISnA)," "To-(PLPSnA)" or "To-(PDLMTSnA)" as a coloriess, transparent solution.

EXAMPLE 8

Distribution of the 99-Tc-labeled radioactive diagnostic agents in the organs of rats

The ***To-labeled radioactive diagnostic agent "To20 ***To-labeled radioactive diagnostic agent "To-In the same manner as in Example 3 but using the (PLISAA)," "To-(PLPSaA)" or "To-(PDLMTSaA)" in place of the 95mTo-labeled radioactive diagnostic agent "To-(PLTSaA)," the distribution in the organs of rats I hour after the administration was examined. The results are shown in Table 4.

TABLE 4

Distribution of To-(PLISAA), To-(PLPSAA) and To-(PDLMTSaA) in organ (% to radioactivity ada

	Organs	To-(FLISaA)	To- (PLPSeA)	To- (FDLMTS=A)	
	Liver	0.69	4.49	1.26	
	Small intention	84.82	81.76	93.00	
- 35	Large intestine	0.04	0.04	0.04	
	Stomach	0.03	0.04	0.06	
	Spices	0.02	0.03	0.04	
	Lung	0.06	0.06	0.07	
	Hout	0.03	0.02	0.02	
	Kidocys	0.39	1.02	0.23	
40	Blood (1 sel) ^a	0.038	0.042	0.028	
•••	Curcus	2.00	2.03	3.17	
	Bladder (Urine)	11.00	9.91	1.70	

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From the above results, it is understood that the 99-To-labeled radioactive diagnostic agents are all treeful for examination of hepatobiliary ducts.

EXAMPLE 9

Stability of the non-radioactive carriers "PLISaA," "PLPSoA" and "PDLMTSoA"

In the same manner as in Example 4, the stability of the non-radioactive carriers "PLISaA," "PLPSaA" and "PDLMTSoA" was examined. As the results, it was confirmed that they are stable even after stored for a period of 100 days or more.

EXAMPLE 10

Subling of the 1. Tool " of the fire of a postice of a po agents "Tc-(PLISaA)", "Tc-(PLPSaA)" and Tc-(PDLMTSoA)"

In the same manner as in Example 5, the stability of the "In To-labeled radioactive diagnostic agents "To-"Tc-(PLTSaA)" and (PDLMTSaA)" was examined. As the results, it was confirmed that they are stable even after stored for a period of 48 hours or more.

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EXAMPLE 11

Toxicity of the non-radioactive diagnostic agents

In the same manner as in Example 1 or 6 but using the materials other than water in amounts of 2 times, there were prepared non-radioactive carriers having 2 fold concentrations in comparison with the concentrations of the non-radioactive carriers as prepared in Example 1 or 6.

The resulting non-radioactive carriers were intravenously administered to groups of SD strain male rats, groups of SD strain female rats, groups of ICR strain male mice and groups of ICR strain female mice, each group consisting of 10 animals, at a dose of 1 ml per 100 g of body weight. (This dose corresponds to 2400 times the normal dose to human beings.) Separately, the same volume of physiological saline solution as above (per unit of body weight) was intravenously administered to the same groups of animals as above for the control.

For 10 days after the administration, the animals were fed, and the change of body weight was daily recorded. No significant reference was recognized between the drug administered groups and the control groups. Then, 25 all the animals were sacrificed and subjected to observation of the abnormality in various organs. But, no abnormality was seen in any of the animals.

From the above results, it may be said that the toxicity of the non-radioactive carrier according to this invention is extremely low.

What is claimed is:

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1. A non-radioactive carrier comprising an N-pyridoxyl-α-amino acid of the formula:

wherein R^4 and R^2 are each an atom or an atomic group 45 present in the α -amino acid residue encompassed by the dotted line and R^3 , R^4 , R^5 and R^6 are each a hydrogen atom, a halogen atom, a C_1 - C_{10} alkyl group or a C_1 - C_{10} alkyl group substituted with at least one hydrophilic group or its salt, and a reducing agent for pertechnetate.

2. The non-radioactive carrier according to claim 1, wherein the N-pyridoxyl-α-amino acid is the one of the formula (I) wherein R³ and R⁵ are each hydrogen, R⁴ is hydroxymethyl and R⁶ is methyl.

3. The non-radioactive carrier according to claim 1, wherein the N-pyridoxyl-a-amino acid is the one of the formula (I) wherein R², R³ and R⁵ are each hydrogen, R⁴ is hydroxymethyl and R⁶ is methyl.

4. The non-radioactive carrier according to claim 1, wherein the N-pyridoxyl-α-amino acid is the one of the formula (I) wherein R¹ is hydrogen, methyl, isopropyl, 1-methylpropyl, 2-carboxyethyl, hydroxymethyl, 1-hydroxyethyl, benzyl or 4-hydroxyben-65

zyl, R², R³ and R⁵ are each hydrogen, R⁴ is hydroxymethyl and R⁶ is methyl.

 The non-radioactive carrier according to claim 1, wherein the N-pyridoxyl-α-amino acid is an N-pyridox yl-tryptophan derivative of the formula:

volume of physiological saline solution as above (per unit of body weight) was intravenously administered to the same groups of animals as above for the control.

For 10 days after the administration, the animals were wherein R⁷, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are each a hydrounit of body weight) was intravenously administered to gen atom, a halogen atom, a C₁-C₅ alkyl group substituted with at least one hydrophilic group.

6. The non-radioactive carrier according to claim 5, wherein the N-pyridoxyl-tryptophan derivative is the one of the formula (II) wherein R⁷, R⁸, R⁹, R¹¹ and R¹² are each hydrogen and R¹⁰ is hydrogen or methyl.

The non-radioactive carrier according to claim 1, wherein the reducing agent for pertechnetate is a stannous salt.

8. The non-radioactive carrier according to claim 1, wherein the reducing agent for pertechnetate is contained in an amount of 0.001 to 1 mol per 1 mol of the N-pyridoxyl-a-amino acid or its salt.

9. The non-radioactive carrier according to claim 1, which is in the form of aqueous solution.

10. The non-radioactive carrier according to claim 9, wherein the concentration of the N-pyridoxyl-α-amino acid or its salt is not less than 20 mmol/liter.

11. A ^{99m}To-labeled radioactive diagnostic agent which comprises ^{99m}To in the form of pertechnetate and the non-radioactive carrier comprising an N-pyridyl-α-emino acid of the formula:

wherein R¹ and R² are each an atom or an atomic group present in the α-amino acid residue encompassed by the dotted line and R³, R⁴, R⁵ and R⁶ are each a hydrogen stom, a halogen atom, a C₁-C₁₀ alkyl group or a C₁-C₁₀ alkyl group substituted with at least one hydrophilic group or its salt, and a reducing agent for pertechnetate.

12. The **Tre-leveled radioactive diagnostic agent to according to close 12, prepared by contacting an aqueous solution containing **Tc, the radioactivity of which is 0.1 to 50 mCi in a volume of 0.5 to 5 ml aqueous solution at the time of administration, in the form of pertechnetate with the non-radioactive carrier.

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